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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/082,476 | 02/20/2002 | Gregory D. May | NAPRO-3 | 4408 |

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| EXAMINER | |
|---|---|
| FREDMAN, JEFFREY NORMAN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1637 | |

DATE MAILED: 03/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/082,476 | MAY ET AL. | |
| | Examiner | Art Unit | |
| | Jeffrey Fredman | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *13-17 and 29-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-17 and 29-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 17, 2006 has been entered.

### *Claim Rejections - 35 USC § 112, second paragraph*

2. The rejection of claims 33-41 under 35 U.S.C. 112, second paragraph, is withdrawn in view of the amendment.

### *Claim Rejections - 35 USC § 112, New Matter*

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 13-17 and 29-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As MPEP 2163.06 notes " If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

Here, the amendment to require that the "oligonucleotide consistes of a single stranded DNA oligonucleotide" is apparently new matter. A careful review by the examiner of the cited pages of the specification failed to identify any support for this limitation.

Applicant points to figures 1A-1D for support as welll as "throughout the specification". Figures 1A-1D all show oligonucleotides with both upper and lower case letters. The specification, at page 7, lines 10-15, indicates that lower case letters are RNA nucleotides. Thus, Figures 1A-1D do NOT provide support for an oligonucleotide which "consists of DNA" because those oligonucleotides are RNA/DNA chimeras. A review of the rest of the specification found no disclosure of any oligonucleotide which was not an RNA/DNA chimera.

Since no basis has been found to support the new claim limitation in the specification, the claim is rejected as incorporating new matter.

***Claim Rejections - 35 USC § 112, Enablement***

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 13-17 and 29-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a cell free composition for modification of DNA sequences. The invention is in an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims are specifically drawn to oligonucleotides which "consist" of single stranded DNA oligonucleotides, to the intended exclusion of RNA/DNA chimeric oligonucleotides. Otherwise, the claims broadly encompass any duplex DNA in plasmids, bacteriophage or bacterial artificial chromosomes and broadly encompass any extract from a plant cell, including any plant whatsoever.

Quantity of Experimenation

The quantity of experimentation in this area is large since there is significant variability in ability of oligonucleotides which consist of DNA to function in DNA modification assays. Identification of specific plant cell extracts which would permit DNA oligonucleotides to function is an inventive, unpredictable and difficult undertaking in itself, and efficacy of DNA oligonucleotides would need to be demonstrated in a variety of different plant cell types. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The prior art specifically states that oligonucleotides which "consist" of DNA do not function in targeted gene correction. Yoon et al (Proc. Natl. Acad. Sci. (1996) 93:2071-2076) notes "The importance of RNA in the present study was demonstrated by the differential activities of oligonucleotides containing identical sequence with or without RNA stretches, Ch1 and Dh1, in eliciting the genetic change detected at both the biochemical (Figs. 2 and 3) and genetic (Fig. 4 and Table 1) levels (see page 2075, column 1)." A look at Table 1 of Yoon shows that the DNA oligonucleotide resulted in a 0% conversion rate, while the Ch1 RNA/DNA chimeric oligonucleotide had a 34-38% conversion rate. This is an express demonstration by the prior art that DNA oligonucleotides will not function in the DNA modification assay. This result is further supported by Baszczynski et al (U.S. Patent 6,528,700), who notes,

> "In addition, as reported in previous studies using chimeric RNA/DNA oligonucleotides in mammalian cells (Yoon et al. (1996) Proc. Natl. Acad Sci. USA 93:2071-2076), Cole-Strauss et al. (1996) Antisense Nucl. Acid Drug Dev.

> 7:211-216, Xiang et al. (1997) J. Mol. Med. 75:829-835, Kren et al. (1997) Hepatology 25:1462-1468 and (1998) Nature Med. 4:285-290), no targeted modifications were observed in cells bombarded with either non-target sequence-specific chimeric oligonucleotides or DNA versions of the target sequence-specific oligonucleotides (see column 19, lines 9-17)."

Thus, oligonucleotides which "consist" of only DNA without RNA do not function to modify DNA sequences.

Working Examples

The specification has no working examples of DNA modification with oligonucleotides which "consist" of DNA.

Guidance in the Specification.

The specification solely exemplifies RNA/DNA chimeric oligonucleotides as shown at page 22, lines 10-17 (paragraph 0051). The specification never discusses oligonucleotides which "consist" of DNA and consequently lack RNA. In fact, the specification only discusses RNA/DNA chimeric oligonucleotides (see pages 1-2, for example).

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability and the teaching against the ability of oligonucleotides which "consist of" DNA as functional in DNA modification assays by the prior art is opposed to patentability (see Yoon and

Baszczynski). The specification provides one with no written description or guidance that leads one to a reliable method oligonucleotides which "consist of" DNA in the place of RNA/DNA chimeras. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Further the specification does not provide guidance to overcome art recognized problems in the use of oligonucleotides which "consist of" DNA. Thus given claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables such as plant cell extract composition, the lack of guidance provided in the specification, the absence of any working examples and the negative teachings in the prior art balanced only against the high skill level in the art, it is concluded that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

***Claim Rejections - 35 USC § 103***

7. The rejection of claims 13-17 and 29-41 under 35 U.S.C. 103(a) as being unpatentable over Yamashita et al (EP 718,404 A2, June 1996) in view of Baszcynski et al (U.S. 6,528,700) is withdrawn in view of the amendment.

***Response to Arguments***

***8.*** Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637
3/17/06